EXPERT REVIEWS

Integrating stereotactic body radiation therapy in stage II/III non-small cell lung cancer: is local control important?

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Ronald C McGarry

Department of Radiation Medicine, University of Kentucky, 800 Rose St, C114C, Lexington, KY 40536, USA
Tel.: +1 859 257 7618
Fax: +1 859 267 4060
ronald.mcgarry@uky.edu

Local control for advanced non-small cell lung cancer (NSCLC) remains a significant problem with chemoradiation local failure rates in the chest of 30–50%. Despite attempts at dose escalation with conventional radiation therapy techniques, toxicities limit the amount of radiation that can be delivered. For stage I NSCLC, mounting evidence supports the use of hypofractionated radiation therapy (SBRT) to gain high local control rates with acceptable toxicity. For healthy patients with stage II/III NSCLC, the National Comprehensive Cancer Network guidelines suggest surgery is the preferred standard of care for patients with <N2 nodes or T3 tumors. In select patients who are surgical candidates or have more extensive disease, guidelines may include pre-operative chemoradiation followed by surgery, although this remains controversial and is the subject of a current national clinical trial (RTOG 0839). Dose escalation through conventional radiation therapy planning suggests that we can improve outcomes in stage III patients, but toxicity remains problematic. It follows that with improvements in imaging and delivery of radiotherapy, dose escalation with SBRT incorporation may improve local control in stage II/III NSCLC for medically inoperable patients. The rationale for dose escalation and some of the considerations for incorporation of SBRT dose escalation in stage III lung cancer are reviewed here.

KEYWORDS: local control • stage III lung cancer • stereotactic body radiation therapy

Non-small cell lung cancer (NSCLC) represents one of the most challenging malignancies to manage in which cure rates have only marginally improved in the past 20 years, with overall 5-year survival rates of 15–17% for locally advanced disease. Approximately 25% of patients present with stage I/II disease, 40% with stage III and 35% with stage IV [1]. For those patients who are surgical candidates and with a technically feasible complete resection, radical surgery remains the standard of care but traditionally those patients with ≥N2 nodal levels or T4 disease are considered inoperable [2,3]. Given that the average age of patients diagnosed with NSCLC is in their mid-60s and usually have long smoking histories, many patients are medically inoperable, usually defined by poor pulmonary reserve, cardiac insufficiencies or other serious comorbidities.

In the early 1980s, the CALGB completed a protocol for the treatment of stage III NSCLC that employed chemotherapy first, which they called 'proto-adjuvant.' This landmark, paradigm shifting trial widely known as the Dillman trial [4] altered the course of non-surgical therapy by demonstrating that treatment regimens including chemotherapy were significantly better than radiotherapy alone. The median survival was nearly 14 months with sequential chemotherapy followed by radiation therapy and only 9 months with radiotherapy alone to 60 Gy [4]. The study was replicated by an Intergroup effort [5]. The radiation dose used in this trial – 60 Gy – remains the standard of care. The primary issue with radiation dose intensification done by conventional 3D planning and dosing is the difficulty in maintaining the dose to vital structures in the chest to acceptable levels to minimize the risk of toxicity such as pulmonary damage (expressed as dyspnea or pneumonitis), esophageal dose with stricture

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formation and cardiac toxicities (e.g., coronary artery damage, pulmonary vasculature damage). Despite the lack of success in escalating radiation doses via conventional techniques to that theoretically needed to improve local control, new technologies in imaging and radiation delivery such PET/CT may assist in assessing the extent of disease and early detection of new metastatic disease. Radiation delivery with volumetric modulated arc therapy-like systems or robotic radiosurgery may exploit 4D imaging to assess tumor motion and image guidance to ensure better targeting of a tumor mass both during setup and from fraction to fraction of treatment.

Can conventional RT treatment fractionation achieve the doses needed for high local control?

Current doses and techniques of standard radiation therapy (RT) result in high local failure rates (between 20 and 50%) that theoretically could act as a nidus for metastasis. While various dose escalation trials have suggested a benefit of increasing the RT dose to obtain better local control, thus far no prospective trials have shown benefit to escalation and some studies actually show a survival detriment to the doses of radiation needed to control the tumor volumes [6–8]. Tolerance of organs such as esophagus, spinal cord and heart are carefully assessed before radiation dose delivery, but the lungs themselves are of primary importance with a commonly considered dose limiting toxicity being pneumonitis. Pneumonitis has a dose volume relationship which is not clearly definable due to the variability in lung physiology (e.g., emphysematous bullae, upper vs lower lobes and even density changes in the normal aging lung) and attempts to develop predictive models for pneumonitis are fraught with difficulties. To predict risk of pneumonitis, we often assess the V_{20} value, basically the volume of lung encompassed by the 20 Gy isodose line in patients receiving standard fractioned radiotherapy (1.8–2.0 Gy/fraction to 60 Gy) [9]. Many cases of pneumonitis occur in patients considered as low risk by V_{20}.

Most strategies for radiation dose escalation try to equate dose/fractionation schemes by employing linear quadratic normalization (biological effective doses [BED]). Applying the linear quadratic equation (BED = nd [1 + d/α/β], where n = the number of fractions, d = the dose/fraction, and an α/β ratio of 10 for acute reacting tissue and tumor cells and a ratio of 3 for late reacting tissues, e.g., spinal cord), 70 Gy will only have a BED of approximately 84 Gy. Using a mathematical model, Martel *et al.* [10] predicted that for NSCLC patients, the dose to achieve significant probability of tumor control and local progression free survival (>30 months) may be at least 84 Gy (100 Gy BED at 2.0 Gy/fraction). The Radiation Therapy Oncology Group (RTOG) 9311 trial was a multi-institutional trial of 179 patients, which attempted to escalate the dose of radiation alone without concurrent chemotherapy [6]. Dose escalation was performed based on the V_{20} volumes determined at the time of planning, that is, the larger the volume of lung receiving 20 Gy, the lower the dose prescribed. Based on this individualized treatment, doses were escalated in bins up to 90.3 Gy in 2.15 Gy fractions. The 90.3-Gy dose level was too toxic, resulting in treatment-related deaths in two patients. Despite not permitting elective nodal coverage, the isolated nodal failure rate was <10%. This study suggested that for patients receiving RT alone or radiation following induction chemotherapy, doses of 83.8 Gy using 3D conformal RT techniques were tolerable in highly selected patients. On a theoretical basis when converted to BED [11], newer data would suggest that this represents a borderline dose of RT to gain a high probability of local control, especially considering that patients who entered these trials were highly selected. Phase II studies from the RTOG (0117), CALGB (Arm 1 of 30105) and North Carolina University groups also showed encouraging median survival times of approximately 24 months with concurrent chemotherapy to 74 Gy being the radiation dose limiting level [8,12,13].

Willner *et al.* [14] retrospectively examined the influence of total dose and tumor volumes on local control and survival, and concluded that there is a dose effect on local control and survival with doses of at least 70 Gy (standard fractionation) and that tumors with volumes ≥100 cc may require higher doses.

In a landmark trial, RTOG 9410 [15] examined two concurrent chemoradiation regimens and one sequential chemotherapy plus thoracic radiation therapy regimen in a three-armed study. In an effort to examine the escalated dose, arm 3 of this trial used concurrent chemotherapy with radiation dose escalated to 69.6 Gy delivered as 1.2 Gy/fraction delivered BID. The results showed that the dose-escalated, hyperfractionated RT regimen was not superior to standard cisplatinum-based chemotherapy combined with daily RT to 60 Gy. Dose intensification by hyperfractionation may be biologically very different from large fraction stereotactic body radiation therapy (SBRT).

Similarly, RTOG 06-17 attempted to answer this question by randomizing patients treated with concurrent weekly carboplatin and paclitaxel ± cetuximab and between 60 and 74 Gy of external beam radiation therapy [7]. Unfortunately, the high-dose arm of this trial had to be closed at interim analysis due to failure of the futility analysis showing a survival benefit. As a result, there remains no prospective trial to demonstrate that delivering radiation in excess of 70 Gy concurrent with chemotherapy is feasible, let alone beneficial [7]. With respect to outcomes, the 0617 high-dose 3D conformal radiotherapy (74 Gy) arm had a survival decrement, compared with the standard dose (60 Gy), and only a marginal improvement in local control rates for these patients with unresectable stage III disease leading to the conclusion that 60 Gy concurrent with chemotherapy remains the standard of care [7].

This unexpected result is currently under analysis and the inferior survival may be due to increased dose to dose-limiting organs although this remains speculative. The only marginally improved local recurrence rates may be expected given that the BED delivered by this conventionally fractionated radiation was <100 Gy BED_{10}, even in the 74 Gy arm, and local failures may be expected.

The crux of the matter: is local control important in NSCLC?

Local failures in the treatment of stage III NSCLC remain in the 25–35% range [7], but in the face of distant metastatic rates of 35–45% is local control important to treatment outcome? Many lung cancer studies currently under consideration are focused on survival. Should local control be considered as another study end point?

Perhaps the most compelling argument to support the hypothesis that local control is important in all stages of lung cancer comes from the long tradition of surgical resection of lung cancer either alone or following chemoradiation for borderline surgical tumors. Most surgeons consider resection as 'the ultimate form of local control.' This is especially important within stage IIIa tumors whose characteristics are highly variable within the staging. Within the NCCN guidelines [2], surgery in stage II/IIIa and selected IIIb patients with NSCLC who are medically appropriate is associated with median survivals of up to 60 months in the setting of complete mediastinal lymph node dissection [3]. As in all trials, the patients eligible for surgery are a select population who are healthy enough for surgery, but also with selected tumors and nodal disease that are technically accessible for the surgeon.

The importance of local control may be considered in the context of early stage (localized stage I) NSCLC. Prior to the advent of SBRT, no suitable standard of care was available for the medically inoperable patient with early stage disease. Clearly, the natural history of untreated stage I NSCLC shows that no treatment has only approximately a 10% 3-year survival [16] and many patients later progress, presenting for palliative treatment of advancing disease. The old standard of 60–66 Gy given to a postage stamp field results in survivals and local control approximately half that of the surgical result. In multiple studies of outcome following definitive radiotherapy for medically inoperable NSCLC, survival was superior for patients with tumors under 3 cm. In a review of the literature, Sibley [17] reviewed the results of 10 studies of the treatment of medically inoperable early stage NSCLC with radiotherapy. All patients received megavoltage radiotherapy to doses >55 Gy and a median dose of 60–66 Gy. Patients in these studies generally had a 15% median long-term survival (5 years), 25% dying of intercurrent disease and 30% dying of metastatic disease. Thirty percent died after local failure only. Grade 3–5 complications occurred in <2% of patients. It is clear from these studies that, although patients who are considered medically inoperable have a significant risk of death from intercurrent disease, the majority of patients died of either local failure or metastatic lung cancer but outcomes were better than no treatment. As such, the question arises, if surgery for stage I lung cancer provides good local control with survival improvements over no treatment or conventionally fractionated radiotherapy, is local control important?

The use of stereotactic body radiotherapy has proven to be effective in the treatment of early stage NSCLC [18–20], with most recent studies showing local control rates in excess of 90%. In a pooled analysis of local control and BED, Mehta *et al.* [21] confirmed that for optimal local control of stage 1 lung cancers, a minimum BED of >100 Gy is required, consistent with observed clinical results. Ohnishi *et al.* [11] demonstrated in an subgroup analysis of the All Japan SBRT trial that significant survival benefits for stage I lung cancer resulted when patients received SBRT doses to a BED_{10} in excess of 100 Gy. Thus, based on multiple SBRT trials, it has been convincingly shown that to control a stage I lung cancer (5 cm or less) doses of RT must achieve a high level that is not approached by the standard dose used in stage III lung cancer, for example, 60 Gy = BED_{10} of 72 Gy, or even that in most radiation dose escalation studies, for example, 74 Gy (BED_{10} = 84 Gy).

Despite the high local control rates with low toxicity risk, unfortunately no randomized prospective trial has been performed to directly compare survival between SBRT and lobectomy for patients with early stage disease.

Can SBRT be integrated into patients with stage II/III disease?

In a discussion of SBRT techniques, large radiation fraction size given to very limited volumes of tissue can have serious ramifications and the treating radiation oncologist must define the target volume with a great deal of attention to detail. Clearly, multiple issues must be addressed including defining both the primary tumor mass dose, size and location, the involved nodal volumes, normal tissue toxicity risk and when to deliver the SBRT dose. We will address each in turn.

The primary tumor mass

There are limited data on the results of boosting the primary tumor with hypofractionated radiation following conventional chemoradiation. In a dosimetric feasibility study, Hepel *et al.* [22] examined CT datasets from five randomly selected patients with stage IIIa NSCLC undergoing definitive chemoradiation. Their strategy was to replan patients to receive 50.4 Gy in 28 fractions followed by an SBRT boost to the primary tumor mass and involved nodes of either 16 or 28 Gy in two fractions. Their plans met all customary constraints and dosimetrically seemed feasible. A clinical trial to test feasibility in patients is planned.

Karam *et al.* [23] similarly reported a retrospective study in which 16 patients presenting with either recurrent lung cancer or stages 1a–IIIb who had been treated with conventionally fractionated CRT to doses ranging from 45 to 60 Gy followed by an SBRT boost on Cyberknife of 20–30 Gy in five fractions. The treatment was tolerated well despite the heterogeneous range of doses and stages of cancer.

Currently, the only clinical feasibility and safety study of the use of SBRT to boost the primary tumor mass is a single-institution feasibility trial that was completed at the University of Kentucky. SBRT techniques were used to boost the radiation dose for residual disease following standard CRT to a BED in excess of 100 Gy [24]. In this trial, patients received

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conventional chemoradiation to 60 Gy followed by an SBRT boost (either 20 Gy at 10 Gy/fraction or 19.5 Gy at 6.5 Gy/fraction). In an effort to allow downstaging of the primary mass, SBRT was delivered approximately 4 weeks after completion of the CRT. 35 patients were enrolled with a primary end point of Grade 3 or higher radiation pneumonitis. Only 4 (11.4%) patients developed acute RP and one (3.1%) patient a late Grade 3 RP. This was much less than the predicted 15-20%, and did not exceed the expected rate for conventional CRT to 60 Gy. Based on this and the limited number of other documented Grade ≥3 toxicities, SBRT as a form of dose escalation following conventional CRT was concluded to be safe. This study was not powered to assess survival, but was a safety and feasibility study for stage II/III patients with nonbulky nodal disease.

The above trial of SBRT boost began with a dose of 10 Gy times two fractions, and this did not differ for medial versus peripheral tumor locations. The combined BED of the CRT and the 20 Gy boost to limited volumes of residual disease achieved a cumulative BED of approximately 110 Gy equivalent. After the first 17 patients were enrolled, there were two isolated occurrences of fatal pulmonary hemorrhage. A subsequent analysis was performed and it was noted that both patients developed hemorrhages in the setting of large cavitary, central recurrences involving the hilum. The central structures including the bronchial walls, pulmonary arteries and aorta were retrospectively reviewed and the doses delivered to these structures were compared as well as the location of the planning target volume to the hilum. Statistically there were no differences dosimetrically between patients who developed a fatal hemorrhage from those who did not. Local recurrence remained the most significant predictor [25]. Due to toxicity concerns, the dose and fractionation scheme was amended to permit a slightly lower cumulative and per fraction dose to be delivered to medial tumors within or touching the zone of the proximal bronchial tree per the RTOG 08-13 definition. A dose of 19.5 Gy in three fractions of 6.5 Gy was chosen to yield a BED of 103.5 Gy when combined with the initial 60 Gy of chemoradiation therapy dose. No additional Grade 3 or higher toxicities were observed for patients treated in the trial.

What about lymph nodes & the mediastinum ('central structures')?

In the Kentucky series of SBRT boost to the primary tumor mass [24], 15/37 patients developed recurrent disease in which regional lymph nodes were implicated as either the primary site of recurrence or as a component with distant metastases. Nonetheless, for conventional radiation therapy, target delineation in NSCLC has evolved to include the primary tumor mass plus only the involved nodal regions from the concept of elective nodal irradiation. Multiple studies have shown that the failure rate outside the involved nodal field is very low. In an early study of 50 nonsurgically treated patients [26] who received concurrent chemotherapy and only radiation to the primary and involved nodal areas to doses of ≥50 Gy, 28% failed in-field with intrathoracic failures out of the treated field occurring in 14%. The author postulated the reasons for their low rate of out of field nodal failures to result from chemotherapy efficacy and perhaps the incidental treatment of nodal regions unintentionally covered in the radiation port [27]. It appears that the level of nodal regions containing metastatic disease can influence outcomes. Subcarinal involvement may be a negative factor compared to other nodal level involvement [27]. Rosenzweig *et al.* [28] reviewed a series of 171 patients who received definitive radiation therapy without elective nodal irradiation using 3D conformal techniques. Only 6.4% failed in the uninvolved nodes. Similarly, Sulman *et al.* [29] examined the frequency of elective nodal failure (ENF) and in-field failure in a large cohort of patients with NSCLC staged with PET/CT and treated with 3D conformal radiotherapy (3D-CRT) that excluded uninvolved lymph node stations. In a similar fashion to other studies, only a 4.3% recurrence of any ENF and a 1.7% recurrence of isolated ENF in patients with NSCLC treated with definitive 3D-CRT without prophylactic irradiation of uninvolved lymph node stations were found.

With current improvements in imaging and staging, the management of lymph nodes in planning CRT in stage III lung cancer thus should largely be confined to involved nodal regions. It follows then that if SBRT dose escalation is incorporated into the radiotherapeutic management of these patients, new strategies that encompass limited mediastinal/hilar nodal volumes are needed. Within the SBRT literature, a 'no fly' zone for hypofractionated radiotherapy for stage I lung cancers was designed based on early results [30]. The results of RTOG 0813 which examines dose escalation for medial stage I lung cancers is awaited and should help validate the significance of the 'no-fly' zone. Postulated toxicities of normal tissues could theoretically be predicted by the structures within and adjacent to the mediastinum such as airways, vasculature (venous and arterial), esophagus, spinal cord and heart. Limitations of doses to the spinal cord and the esophagus are regularly considered during virtually all radiotherapy regimens. SBRT radiotherapy dose limits to heart remain problematic due to how to define heart volumes and the rare reported incidence of RT-related side effects, perhaps due to the overall poor outcome of patients with stage III NSCLC.

Fatal pulmonary hemorrhage is a relatively poorly documented cause of death in lung cancer patients possibly because patients with local failure commonly are referred for hospice. As a result, rates have been estimated to be between 1.5 and 3.5% for all patients; however, incidence rates can be as high as 36% in certain situations such as necrotizing squamous cell carcinomas and in the setting of diffuse alveolar damage or infiltration [31]. The anti-angiogenic agent bevacizumab has been implicated in cases [32]. Within the early stage NSCLC literature, pulmonary hemorrhage is rare and contributed to the 'no-fly' zone concept [30].

The question of how much dose the pulmonary vasculature can tolerate is best illustrated by the use of high dose rate brachytherapy for recurrent disease, for which historical rates of

significant pulmonary bleeds are between 4 and 32% [33]. Two applications of 15 Gy prescribed to 6 mm depth results in approximately a 5% rate for fatal hemorrhages [33]. In the setting of recurrent disease among patients treated upfront with conventional RT, it appears that local failure perhaps combined with high doses of radiation may produce fatal hemorrhage rates of a similar magnitude of frequency. Vascular complications following Gamma Knife (Elekta Instruments Inc., Stockholm, Sweden) cranial radiosurgery have been documented after doses as low as 25 Gy, and may occur in a dose-dependent fashion [34–36]. At lower doses such as 20 Gy, animal models using Gamma Knife radiosurgery suggest the majority of injury occurs in the microvasculature, while as doses in excess of 100 Gy, endothelial cell disruption no longer seems restricted to capillaries, as changes begin to involve small-, medium- and large-sized arteries [36]. Higher rates of injury to larger caliber vessels and more extensive wall necrosis may be associated with high radiation fraction size. Rapid tumor growth leading to infarction and cavitation likely plays a major accelerating role for the risk of fatal hemorrhage considering tumor recurrence and cavitation seem to be dominating risk factors [25,31,37]. With respect to single fraction radiation to the hilum, Tinnel *et al.* [38] escalated single fraction radiation to the rat hilum using a Gamma Knife technique delivering 20, 40 and 80 Gy using both 4- and 8-mm collimators. No significant tissue injury was noted until a threshold dose of 80 Gy using the larger 8 mm collimator was applied. At that dose, pathological changes such as pulmonary edema, fibrosis or vascular injury were observed. This would suggest a dose limiting BED for single fraction radiation therapy would exceed 200 Gy, much higher than most SBRT fractionation schemes. Important questions to consider when evaluating the large fraction doses of SBRT include volume effects and apparent dose. One reason SBRT seems to be well tolerated is that we limit the volume of tissue treated in the high dose region limiting the risk of symptomatic toxicity resulting from damage. Historically, these large fraction sizes were associated with high toxicity levels to the point where the initial SBRT studies received much skepticism based on toxicity risk but it appears that the approach of using multiple beams to 'spread out the dose' along with very conformal treatments accounts for the high effectiveness with limited toxicity of SBRT. With respect to doses as expressed in BED, this was a concept based on the linear quadratic survival curves seen experimentally in tissue culture but this relationship may break down in the case of fractions >6 Gy although this remains controversial. Most investigators delivering SBRT use the calculated BED based on the linear quadratic formula recognizing it may not perfectly model the doses tissues are receiving [39].

In a retrospective look at patients treated with SBRT boost in the University of Kentucky trial, a fatal hemoptysis rate of 5% (2/37 patients) and dose/volume limits to a vascular organ at risk was proposed despite the suggestion that the bleed was more related to local recurrence [25]. It was proposed that during treatment planning, the pulmonary vasculature should be contoured at the arterial phase of contrast enhanced vessels to the level of the distal bifurcation of the left and right pulmonary arteries. Since the observed toxicities were considered late developing, the maximum radiation dose to the pulmonary artery should be restricted to less than 185 Gy cumulative BED_3 and to less than 120 Gy for the 5 cc volume, and the maximum dose to the bronchial wall should be limited to less than 175 Gy BED_3.

How can we define the involved nodal regions in the chest?

In the era of improved imaging being incorporated into 3D treatment planning for lung cancer radiation therapy, it appears that staging PET/CT shows more advanced disease and prevents inappropriate surgery in up to 15% of patients. Due to concerns about false-positive results and other issues, PET/CT along with endobronchial ultrasound and esophageal ultrasound or more invasive mediastinoscopy [40] is being used to define the grossly tumor involved lymph nodes in the mediastinum. It is clear from the previous discussion that if SBRT is to be incorporated into boost therapy for node-positive patients, a very careful assessment of the hypofractionated doses used and tolerable volumes is important. PET/CT alone is an effective tool to help define these volumes, but there are technical issues with PET/CT scans themselves.

Standardized uptake values (SUV) have served as a useful semiquantitative index to objectively measure the intensity of flurodeoxyglucose uptake in PET/CT scans. Cautious optimism was expressed by Keyes [41] in 1995 about the utility of SUV in PET, and subsequent publications have utilized SUV in an attempt to quantify tumor response to therapy among other uses [42]. Adams *et al.* [43] have concluded that when SUV comparison is performed to assess response to therapy, imaging should be performed using the same scanner and same image acquisition and reconstruction protocols. SUV remains only semiquantitative and in a similar fashion depends on the skill of the reading physician and patient factors, for example, blood glucose levels. It is therefore contingent on the treating team to consider carefully these factors in using flurodeoxyglucose-PET/CT ± more invasive mediastinal staging to define nodal volumes being treated.

Timing of dose delivery on local control

In considering local control issues, radiobiology would suggest that the length of time taken to deliver the complete dose of RT is important in local control as is the total dose expressed in BED. Accelerated repopulation has been postulated to be a potent source of local failure and is a basic tenet of radiation oncology [44]. Accelerated repopulation in squamous cell head and neck cancers is postulated to occur with a burst of rapid cell division commencing 3–5 weeks after the start of radiation. For treatment schemes beyond this time frame, a dose increment of approximately 60 cGy/day is needed to compensate for this repopulation [45]. The length of time of treatment delivery for head and neck cancers has been considered important for local control considerations [45]. As a result of these

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observations, alternative fractionation schemes were developed for head and neck malignancies that delivered the radiation dose in a timely fashion. Similarly, within the gynecologic literature, it is convincingly shown that the treatment of cervical cancer has superior outcomes if the full radiation dose (including brachytherapy implants) is delivered within a 6-week time frame [46]. Most altered fractionation schemes are limited by acute and late normal tissue toxicities.

The standard course of radiation therapy given to patients with local advanced NSCLC is delivered over a 6-week time frame. One could postulate that the high post-radiotherapy local failure rates in NSCLC could be due to the cumulative dose delivered being inadequate, but also that attempts at dose escalation by delivery of radiation in standard fraction size over a prolonged period is also inadequate to overcome accelerated repopulation. Accordingly, it could be postulated that the length of time of delivery of the high doses of radiation needed to control a lung tumor mass needs to be carefully considered. Accelerated radiotherapy has been considered in several clinical trials. For example, the MRC conducted trials of continuous hyperfractionated accelerated radiation therapy (CHART). Between 1990 and 1995, a total of 563 patients with stage I–III NSCLC were entered into a multicenter randomized controlled trial comparing CHART with conventional (60 Gy/30 fractions) radiotherapy [47]. The 2-year survival rate was improved from 20% with conventional radiotherapy to 29% with CHART [47,48]. Patients in these trials included all stages of NSCLC from one to four. Similar findings have been reported in other small accelerated fractionation trials that are promising, but concerns about increased toxicity have limited its widespread adoption. Thus, in any consideration of dose escalation with a goal of improving local control, the factor of timely delivery of the total dose of radiation therapy should be considered. In incorporating SBRT for the dose escalation of radiation therapy for NSCLC, the delivery of dose must be prompt, either immediately following standard radiation therapy delivery or concurrent in the last week of treatment.

Can SBRT be incorporated as a boost in stage II/III lung cancer?

Multiple studies have been tantalizing in that they suggest that radiation therapy dose escalation may improve overall outcome in survival and local control. It becomes clear that a new approach to dose escalation of radiation therapy in the treatment of these locally advanced patients is necessary. If surgical excision of the primary tumor and lymph node dissection improves outcome in stage II/III lung cancer in patients who are medically fit, the same reasoning could apply to all stage II/III patients with improved radiation technology dosing concepts that could produce similar levels of local control in the chest. The benefit from such less invasive treatment potentially could be extended to all stage II/III patients.

Can we extend the excellent results from SBRT treatment of stage I lung cancer to improve outcomes in more locally advanced disease? From the above discussion, incorporation of hypofractionated radiation to dose escalate stage II/III lung cancer is feasible, but there are many considerations. Based on the dosimetric study of Hepel *et al.* [22] and a single institution study from the University of Kentucky, using SBRT to boost the primary tumor to a BED >100 Gy appears safe and feasible [24].

Local treatment failure considerations may involve both the primary tumor mass and the involved lymph nodes. As a result, both of these areas should be considered for hypofractionated dose escalation aka SBRT. Newer technologies in linear accelerator design and image guidance should allow dose escalation of the primary tumor mass and the involved mediastinal nodes independently. For example, with robotic radiosurgery or arc-based linear accelerator planning of SBRT doses, more than one isocenter could be defined, for example, dose to primary mass versus lymph nodes could differ. We postulate that following standard of care chemoradiation to at least 60 Gy, the addition of highly conformal hypofractionated boost radiation ('SBRT') designed to increase the cumulative BED_{10} dose to at least 80 Gy to involved mediastinal lymph nodes and 100 Gy to the primary tumor will not increase the rate for significant toxicity to >20% and will result in improved progression free survival for patients with selected stage II/III NSCLC. Initially, a rational trial to accomplish this through a Phase I dose escalation of the mediastinal dose independent of the primary tumor volume will require careful estimation of dose to organs at risk and appropriate patient selection with limited nodal volumes.

Expert commentary

The optimal treatment of locally advanced (stage III) NSCLC remains poorly defined. Stages II–III NSCLC are very heterogeneous in terms of extent of disease (T stage, N stage) which makes the 'one size fits all approach' unfeasible. The issues can be broken down into patient factors, for example, healthy patient fit for surgery, radiation or chemotherapy and symptoms (hemoptysis at presentation, superior vena cava syndrome, pain) and disease factors, for example, extent of primary, location, nodal status and mutational analysis. When one looks at disease outcomes after treatment, considerations must include long-term toxicity of treatment (any or all of surgery, radiation and chemotherapy), risk of recurrence in the chest (clear margins after surgery, nodal status and failure to control the primary tumor) and risk of metastasis. All of the above issues generate their own treatment proponents favoring one modality over the other and as such progress is made in small increments. With respect to surgery, for healthy patients, surgery represents an excellent modality of local control, while for more advanced patients many champion the idea that neoadjuvant chemotherapy is ideal since it addresses both local control (CRT/surgery) and theoretically disseminated disease (chemotherapy). While initial data show a little to no benefit to this approach, current trials are underway to extend this idea. What about a patient who is not medically fit or refuses surgery? The issues of radiation therapy are complex and puzzling since the clues that increasing doses of radiation kills more logs of cancer

cells resulting in lower local recurrence rates. Given the experience with improved outcomes with the local control that surgical resection confers (and perhaps more accurate staging information), dose intensification of radiation may play a role in the outcomes of these patients. Our clinical staging has improved significantly with PET/CT, endobronchial/endoesophageal ultrasound and histopathological markers, making the ability to dose intensify the larger volumes of cancer by highly conformal hypofractionated radiation more feasible. These large fractions of radiation, when carefully targeted, have been shown to be very effective in early stage disease and perhaps overcome intrinsic radiation resistance such as hypoxia. Similarly, for those patients who have recurrence of disease or who are not surgical candidates, the search for targeted chemotherapy agents along with mutation analysis may result in improvements in management of metastatic disease. In summary, improvements in outcomes of patients with locally advanced disease need to be studied in all modalities in an effort to move forward.

Five-year view

Locally advanced lung cancer has been problematic with respect to our failure to show significant improvements in survival for many years. 'Curative' radiation has improved with respect to outcome when combined with chemotherapy but has been frustrated by our inability to achieve the doses of radiation needed for meaningful improvements in local control. The advent of SBRT with its high dose per fraction of carefully targeted radiation has been a success story in stage I lung cancer but needs to be translated to more locally advanced cancers in a logical way. We have the basis for the appropriate clinical trials to address this innovative technique but it will take at least 5 years to begin to fully assess whether there is a benefit to it. From the SBRT trials for early stage lung cancer, we can infer the appropriate dose levels we need to achieve to result in improved local control for our more commonly seen locally advanced patients. On a more controversial level, if screening of high-risk patients is generally accepted, we may see a stage migration away from the most common locally advanced patient we presently treat to earlier potentially curable lung cancers. The cost of screening and treatment remains an issue that may be unresolved for years to come. Optimistically, we hope that in 5 years both screening and improved treatment may improve the outcome of a difficult disease.

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Key issues

- Patients with inoperable node-positive or locally advanced lung cancer treated with chemoradiation have significant rates of local failure.
- The selected patients who are surgical candidates have improved local control and survival.
- Dose escalation studies have suggested that increased radiation dose may result in improved outcome but are hampered by toxicities.
- Stereotactic body radiation therapy for early stage lung cancer has a high level of local control with low toxicity risk.
- Thus the key question is what factors need to be considered in translating the excellent results of stereotactic body radiation therapy to the treatment of locally advanced or node-positive lung cancers for improving nonsurgical treatment of these patients.

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• **The older CALGB 8433 trial set radiotherapy parameters we now consider standard of care.**

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